

# Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics

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**Abstract:** Complicated skin and soft tissue infections (cSSTIs) represent the severe form of infectious disease that involves deeper soft tissues. Involvement of methicillin-resistant *Staphylococcus aureus* (MRSA) further complicates cSSTI with increased hospitalization, health care costs, and overall mortality. Various international guidelines provide recommendations on the management of cSSTIs, with the inclusion of newer antibiotics. This literature-based review discusses the overall management of cSSTI, including appropriate use of antibiotics in clinical practice. Successful treatment of cSSTIs starts with early and precise diagnosis, including identification of causative pathogen and its load, determination of infection severity, associated complications, and risk factors. The current standard-of-care for cSSTIs involves incision, drainage, surgical debridement, broad-spectrum antibiotic therapy, and supportive care. In recent years, the emergence of newer antibiotics (eg, ceftaroline, tigecycline, daptomycin, linezolid, etc) has provided clinicians wider options of antimicrobial therapy. Selection of antibiotics should be based on the drug characteristics, effectiveness, safety, and treatment costs, alongside other aspects such as host factors and local multidrug resistance rates. However, larger studies on newer antibiotics are warranted to refine the decision making on the appropriate antimicrobial therapy. Local Antimicrobial Stewardship Program strategies in health care settings could guide clinicians for early initiation of specific treatments to combat region-specific antimicrobial resistance, minimize adverse effects, and to improve outcomes such as reduction in *Clostridium difficile* infections. These strategies involving iv-to-oral switch, de-escalation to narrow-spectrum antibiotics, and dose optimization have an impact on the overall improvement of cSSTI therapy outcomes, especially in countries like Singapore that has a high disease burden.

**Keywords:** antibiotics, complicated skin and soft tissue infections, methicillin-resistant *Staphylococcus aureus*, Singapore

## Introduction

Skin and soft tissue infections (SSTIs) encompass a wide clinical spectrum of common infectious diseases that often require acute treatment and inpatient hospital admission. These infections have a heterogeneous manifestation and involve microbial infection of the epidermis, dermis, superficial fascia, subcutaneous tissues, and muscle in an increasing order of severity.<sup>1</sup> Complicated SSTIs (cSSTIs) are the most severe, involving deeper soft tissues and include infective cellulitis, ulcer or wound site infections, surgical site infections, major abscesses, infected burns, skin ulcers, and diabetic foot ulcers.<sup>2</sup> The US FDA in 2013 grouped all SSTIs under a unified term, Acute Bacterial Skin and Skin Structure Infection (ABSSSI), which includes cellulitis/erysipelas,

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wound infection, and major cutaneous abscesses. It is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm<sup>2</sup> (lesion size measured by the area of redness, edema, or induration).<sup>3</sup>

*Staphylococcus aureus*, an aerobic Gram-positive coccus, is the most dominant causative pathogen and has paramount epidemiological significance in cSSTI. *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterococcus* spp. have also been identified as causes of cSSTI; however, these are not the predominant causative pathogens.<sup>4</sup> The rampant emergence of methicillin-resistant *S. aureus* (MRSA) infections, endemic to several countries worldwide, has confounded the treatment of cSSTIs.<sup>5</sup> Initially, as MRSA emerged (from 1961 to 1990), hospital-associated MRSA (HA-MRSA) predominated, but in recent years, preponderance of community-associated MRSA (CA-MRSA) in SSTIs is noted in the US and Europe.<sup>6,7</sup> Dense population and relatively greater indiscriminate use of antibiotics predisposes Asian countries to high prevalence of endemic MRSA with estimated proportions of up to 70%.<sup>8</sup> A multinational surveillance study conducted across eight Asian countries, namely, Korea, Taiwan, Hong Kong, Thailand, the Philippines, Vietnam, India, and Sri Lanka, from September 2004 to August 2006 showed increase in the emergence of CA-MRSA, with incidence ranging from 2.5% to 39%.<sup>9</sup>

The epidemiology of MRSA infections reflects the overall increasing burden of SSTIs worldwide.<sup>10,11</sup> In Asia, variable rates of MRSA (7.3%–74%) are reported in patients with SSTIs tested positive for *S. aureus*.<sup>12–17</sup> In Singapore, high rates of MRSA (35.3%) were reported among *S. aureus* isolates, generally comparable with Western countries (23.6%–73.8%).<sup>18,19</sup> Also, the SSTI-associated nosocomial infections account for 7.2% of all hospital-associated (HA) infections, with *S. aureus* identified as the predominant pathogen (27%).<sup>20</sup> MRSA is a common cause of nosocomial infections in Singapore with incidences of serious outbreaks reported in general hospitals and intensive care units.<sup>21–23</sup> Additionally, elderly patients and patients with skin lesions or dermatological conditions were noted with a higher risk of harboring MRSA.<sup>23</sup> The looming danger of severe infectious diseases like cSSTIs and the associated microbial resistance are persuasive, underscoring the need for implementation of systematic surveillance of cSSTI in Singapore. Several international working groups provide guidance on the surgical and pharmacological management of cSSTIs recommending inclusion of recently approved newer antibiotics. However, local data from Singapore for the prudent use of antibiotics in cSSTIs are scanty. The review, therefore, aims to provide an overview of the microbiology, drug resistance

issues, diagnosis, and the overall management of cSSTI. In particular, the review explores the current medical evidence for appropriate use of antimicrobials and current management strategies for cSSTIs to achieve the best clinical outcomes, with special focus on newer antibiotics, which are approved by US FDA after 2000.

## Literature search methodology

An electronic search of PubMed was conducted to source relevant articles using a combination of MeSH terms “complicated skin and skin structure infections”, “skin and soft tissue infections”, “Gram-positive pathogens”, “*Staphylococcus aureus*”, “methicillin-resistant *Staphylococcus aureus*”, “MRSA”, “multi drug resistance”, “nosocomial infections”, and “community-acquired infections”. Relevant articles included randomized controlled trials, surveillance, outcome studies, and expert opinions. Bibliographies of relevant articles were manually screened to broaden the literature search. All articles were restricted to English language and no restrictions were set with respect to year or type of publication.

## Microbiology of cSSTI

Invasion of pathogens through disruptions of skin or soft tissue structure is the fundamental etiology of SSTIs and several local and systemic risk factors further increase vulnerability to cSSTIs (Table 1).<sup>24</sup>

*S. aureus*, *P. aeruginosa*, *E. coli*, *Enterococcus* spp., *Enterobacter* spp., *Klebsiella* spp., and  $\beta$ -*Streptococcus* are the frequently encountered pathogens causing SSTIs in hospitalized patients.<sup>19</sup> cSSTIs may be monomicrobial or polymicrobial in nature with increased systemic inflammatory responses. Management of polymicrobial or mixed infections requires a multidrug approach that is effective against aerobic, anaerobic, and facultative bacteria.<sup>25</sup> Diabetic patients are at twice the risk vs non-diabetics, for cSSTI-related hospitalizations.<sup>26</sup> In cases where vascular circulation is compromised such as diabetic foot infection, or infection of ischemic or venous ulcers, the risk of polymicrobial infections is high. These complications are more common in patients who had previously received antibiotics for chronic infections.<sup>27</sup>

## Issues related to the emergence of multidrug-resistant cSSTI and pertinent clinical management issues

The empirical approach for the treatment of cSSTI uses a combination of surgical, supportive, and antimicrobial

**Table 1** Skin and soft tissue infections: risk factors and common causative pathogens

Risk factors	
Local	Systemic
<ul style="list-style-type: none"> <li>• Soft tissue trauma</li> <li>• Animal or human bites</li> <li>• Burns</li> <li>• Operative or highly contaminated wounds</li> <li>• Diminished perfusion due to peripheral vascular disease, obesity</li> <li>• Poor hygiene</li> <li>• Exposure to contaminated water</li> <li>• Presence of foreign body (eg, piercing, tattoos)</li> <li>• Venous insufficiency and stasis</li> </ul>	<ul style="list-style-type: none"> <li>• Poorly controlled diabetes mellitus</li> <li>• Immunocompromised comorbidities (eg, HIV infection, cellular or humoral immune deficiencies)</li> <li>• Concomitant drugs (ie, corticosteroids, cyclosporine)</li> <li>• Sensory neuropathies</li> <li>• Chronic systemic illness (eg, cirrhosis)</li> </ul>
Infection or risk factor	Causative pathogen
<b>Abscess</b>	<i>Staphylococcus aureus</i>
	Polymicrobial
<b>Cellulitis</b>	<i>S. aureus</i>
	GABHS
	<i>S. aureus</i>
Associated with injection use	<i>Aeromonas hydrophila</i> , <i>Vibrio vulnificus</i> , <i>Mycobacterium marinum</i>
Associated with water exposure	<i>Pasteurella multocida</i> , <i>Capnocytophaga canimorsus</i>
Associated with animal bite	Human oral flora
Associated with human bite	Anaerobes
<b>Surgical site infections</b>	<i>Enterococcus</i> spp.
	<i>Enterobacter</i> spp.
	Gram-negative bacilli
	<i>Staphylococcus</i> spp.
	<i>Streptococcus</i> spp.
	<i>Escherichia coli</i>
<b>Necrotizing fasciitis</b>	<b>Monomicrobial:</b>
	<i>S. pyogenes</i> , <i>S. aureus</i> , <i>Enterobacteriaceae</i> , <i>Bacteroides</i> , and <i>Peptostreptococcus</i> species
	<b>Polymicrobial:</b>
	<i>Clostridium perfringens</i> , <i>S. aureus</i> , <i>Pseudomonas aeruginosa</i>
	<i>C. perfringens</i>
<b>Myonecrosis</b>	MRSA
<b>Recurrent hospital admissions</b>	<i>S. aureus</i> (MRSA and MSSA), GABHS, anaerobes, Gram-negative bacilli
<b>Diabetes</b>	<i>S. aureus</i> , <i>Enterococcus</i> spp., <i>Streptococcus</i> spp.
Diabetic foot ulcers	<i>P. aeruginosa</i> , <i>Enterobacter</i> spp., <i>Acinetobacter</i> spp.
	<i>Bacteroides</i> spp
<b>Cirrhosis</b>	<i>Campylobacter fetus</i> , <i>Klebsiella pneumoniae</i> , <i>E. coli</i> , <i>Capnocytophaga canimorsus</i> , other
	Gram-negative bacilli, <i>Vibrio vulnificus</i>
<b>Neutropenia</b>	Gram-negative bacilli, <i>P. aeruginosa</i>

**Abbreviations:** GABHS, group A  $\beta$ -hemolytic streptococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

therapies. However, a rise in antibiotic-resistant microorganisms,<sup>27</sup> particularly multidrug-resistant organisms, has complicated the treatment of cSSTI. Among multidrug-resistant organisms, MRSA, vancomycin-resistant *Enterococcus* spp. (VRE), and extended-spectrum  $\beta$ -lactamase (ESBL)-producing isolates of *E. coli* and *Klebsiella* spp. have the highest occurrence.<sup>19</sup> Factors contributing to the development of MRSA SSTIs are intravenous drug use, HIV seropositivity, MRSA colonization or previous infection, African-American race, indwelling devices, and previous antibiotics or hospitalizations.<sup>11,28</sup> The strains of CA-MRSA are genetically and

phenotypically distinct from HA-MRSA, and hence possess a risk of infections having greater severity and easier transmission of resistance.<sup>29</sup> The presence of Panton-Valentine leucocidin, a cytolytic toxin, encoding genes in MRSA isolated from CA-SSTIs are postulated to play a significant role in the increased virulence of these strains and are associated with tissue necrosis, and greater severity of local and systemic manifestations.<sup>5,29</sup> The CA-MRSA strains also carry the staphylococcal cassette chromosome mec (SCCmec) genes (types IV and V) that confer resistance to methicillin and currently available  $\beta$ -lactam antimicrobial agents and aid

easy transfer of resistance between organisms.<sup>30</sup> Although MRSA was considered to be chiefly an HA infection, recent evidence suggests rapid emergence of CA-MRSA even in hospital settings.<sup>31–33</sup> This complex infection epidemiology trend has further complicated the selection of antibiotics for treatment of cSSTI.

## Diagnosis of complicated skin and soft tissue infections

Accurate diagnosis involving assessment of complications, severity, and risk factors, followed by identification of causative microorganism is essential for the management of cSSTI.

Comprehensive diagnosis of cSSTIs often starts with a clinical history and findings from physical examination that help assess the severity of an infection followed by investigation of causative microorganism and its load. The precise diagnosis subsequently guides the decision on prompt and appropriate treatments<sup>34,35</sup> (Figure 1).

Standard laboratory investigations are performed to augment clinical assessment, especially for inpatients. In addition to the patient history, relevant risk factors such as recurrent hospital admissions, diabetes, neutropenia, bite wounds, and

animal contacts should be taken into consideration, which may indicate the possible microorganism responsible for the infection.<sup>27</sup> Complications likely related to cSSTIs such as lymphadenitis, myositis/necrotizing fasciitis, gangrene, osteomyelitis, bacteremia, endocarditis, septicemia, or sepsis must also be factored in during diagnosis.<sup>36</sup> The presence of significant leucocytosis (or leucopenia) may potentially indicate sepsis syndrome, while elevated creatine kinase (CK) levels may be suggestive of myonecrosis caused by necrotizing fasciitis or a compartment syndrome.<sup>27,34</sup> Radiological examination and imaging aid investigations of deep tissue infections to assess site and size of infection and any vascular involvement that can guide surgical drainage procedures. Microbiological culture tests should be performed in all cases to differentiate MRSA cSSTIs from non-MRSA infections and thus refine the decision on the definitive antibiotics administration to minimize the risk of potential treatment failure.<sup>35,37</sup>

Accurate diagnosis of cSSTIs can be an indicator of appropriate referrals in addition to immediate hospitalization. Observation of limb-threatening infections in patients with diabetes should prompt urgent referral to a multidisciplinary team, including infectious disease experts, podiatry, and/or

### Physical signs

- Bullae, hemorrhagic lesions, anesthesia or extreme pain, redness, warmth, swelling and tenderness
- Markers of increasing severity of infection
  - Sepsis, fluctuance in abscess, crepitus (sign of necrotizing fasciitis)
  - Systemic manifestations: hypotension, tachycardia, body temperature  $<35^{\circ}\text{C}$  or  $>40^{\circ}\text{C}$ , and confusion or decreased levels of consciousness

### Standard laboratory tests

- Complete blood count
- C-reactive protein
- Creatinine
- Bicarbonate
- Creatine phosphokinase

### Radiological examination

- X-ray
- Computed tomography
- Doppler vascular examination
- Magnetic resonance imaging

### Microbiological examination (Culture)

- **Open wounds:** Tissue specimens
- **Ulcerated skin:** Tissue biopsy or curettage
- **Non-open wounds:** Needle aspiration
- **Sepsis syndrome or severe infections:** Blood culture

**Figure 1** Diagnosis of complicated skin and soft tissue infections.

surgical (eg, orthopedic, vascular) specialists for effective surgical consultation and appropriate antimicrobial use.<sup>34</sup> Surgical consultation might also be required in cases of infections such as necrotizing fasciitis, synergic gangrene, and osteomyelitis or septic arthritis.

## Management of complicated skin and soft tissue infections

The three fundamental pillars of cSSTI management are surgical drainage with debridement where necessary, broad-spectrum antibiotic therapy, and physiological supportive care (Table 2).<sup>27,31</sup> These interventions together are necessary to ensure effective cSSTIs management, especially for a disease with diverse clinical presentation and dynamic interplay of multiple microbial, host, and local factors. The goals of cSSTI treatment are source control, antimicrobial therapy, and organ supportive care. Source control achieved by debridement only facilitates wound healing process that may be managed further by pharmacological interventions.<sup>38</sup>

## Surgical methods and supportive care

Exudates, fluid collections of abscess, and ulcerations are common features of cSSTIs. Therefore, aggressive surgical debridement of the necrotic/infected tissue using chemical or mechanical methods is preferred whenever feasible to arrest the spread of infection and promote wound healing (Table 2). Delay in definitive debridement of necrotizing soft tissue

infections is known as the single most significant risk factor for death.<sup>39</sup> Incision and drainage are performed for abscess and purulent infections.<sup>40</sup> Other approaches include topical negative pressure (TNP) dressing for chronic infections or large wounds with excessive exudate,<sup>35,41</sup> vacuum-assisted closure (as alternative for wound healing) especially for surgical wounds or post-surgical deep infections,<sup>41</sup> thrombectomy for infections involving septic venous thrombosis, and reconstructive revascularization for cases involving arterial vessel injuries.<sup>42</sup> Supportive cares involving fluid resuscitation, organs support, and nutritional management to maintain oxygenation and tissue perfusion are critical interventions in the clinical outcomes of these patients.<sup>35,39</sup>

## Pharmacological management

Systemic antibiotic therapy against the causative pathogen remains the mainstay for treatment of cSSTIs. Antibiotics against *S. aureus* are recommended for all cases involving systemic presentations such as temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , tachypnea ( $>24$  breaths per minute), tachycardia ( $>90$  beats per minute), or white blood cell count (WBC)  $>12,000$  or  $<400$  cells/ $\mu\text{L}$ .<sup>40</sup> Most eminent international guidelines recommend initial management with empirical antibiotic therapy against locally prevalent MRSA strains. The Infectious Diseases Society of America recommends bacterial culture assessment to aid the selection of antibiotics against the causative pathogens and initiate definitive therapy

**Table 2** Recommendations for antibiotic treatment of methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections

Guidelines	Infection	Recommended therapy
Infectious Diseases Society of America <sup>31</sup>	cSSTI (deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns) Non-purulent cellulitis	<ul style="list-style-type: none"> <li>Surgical debridement</li> <li>Vancomycin, linezolid, daptomycin, telavancin, clindamycin</li> <li><math>\beta</math>-lactam antibiotic active against MRSA</li> </ul>
Surgical Infection Society <sup>18</sup>	Complex abscesses with cellulitis and polymicrobial cSSTIs	<ul style="list-style-type: none"> <li>Incision and drainage (in case of abscess)</li> <li>Vancomycin, clindamycin, linezolid, or erythromycin</li> </ul>
Gruppo Italiano di Studio sulle Infezioni Gravi <sup>41</sup>	MRSA-related cSSTIs and severe surgical infections	<ul style="list-style-type: none"> <li>Use of TNP/VAC (for deep surgical infections)</li> <li>Vancomycin, teicoplanin, linezolid, tigecycline, daptomycin</li> </ul>
Italian Society of Infectious Diseases and international Society of Chemotherapy <sup>19</sup>	MRSA-related cSSTIs	<ul style="list-style-type: none"> <li>Early surgical treatment wherever feasible</li> <li>Vancomycin, teicoplanin, linezolid, tigecycline, daptomycin</li> </ul>
Spanish Society of Chemotherapy <sup>35,120</sup>	MRSA-related cSSTIs	Linezolid, daptomycin, vancomycin, teicoplanin
British Society of Antimicrobial Chemotherapy <sup>121</sup>	Severe cSSTI with MRSA	Linezolid, daptomycin, vancomycin, teicoplanin

**Abbreviations:** cSSTIs, complicated skin and soft tissue infections; MRSA, methicillin-resistant *Staphylococcus aureus*; TNP/VAC, topical negative pressure/vacuum-assisted closure.

for severe infection, non-responsiveness to the current line of antibiotics, or recurrent infections.<sup>40</sup> The UK's National Institute for Clinical Excellence also recommends monitoring of clinical progress and reassessment of treatment based on culture findings.<sup>43</sup>

The timing of initiation and choice of appropriate antimicrobial therapy against the causative organism are critical determinants of treatment outcome. Delay in initiating treatment within 8 hours of presentation of cSSTI is associated with longer hospital stays<sup>44</sup> and lack of active antibiotic therapy within 48 hours of admission with treatment failure.<sup>45</sup> The US FDA suggests evaluation of clinical response to antibiotics in ABSSSI within 48–72 hours after initiation of therapy to identify potential treatment failure.<sup>3</sup> In a large study, treatment failure in 22.8% patients with cSSTIs was associated with an increased risk of mortality (OR: 2.91; 95% CI: 2.34–3.62).<sup>46</sup> Prolonged hospital stay or readmission and associated increase in health care cost due to inadequate initial antimicrobial therapy for cSSTI are also reported.<sup>46,47</sup>

Successful therapy requires clinical acumen of empiric and definitive treatment substantiated with knowledge of pharmacokinetic and pharmacodynamic properties of the antibiotics. Minimum inhibitory concentration (MIC) helps interpret susceptibility of the particular pathogen to the antimicrobial agent and rising MICs is indicative of emerging resistance of the pathogen to antibiotics (Table 3). Hence, the antibiotic should achieve a concentration equal to or greater than MIC at the site of infection.<sup>35</sup> Poor tissue penetration adversely impacts the clinical and microbiological treatment outcomes and increases the risk of resistance among pathogens.<sup>48</sup> Several factors such as vascular insufficiency or presence of comorbid diabetes or vascular diseases predominant in cSSTIs are known to interfere with antibiotic tissue penetration, thus restricting their efficacy.<sup>49,50</sup> Hence, for antibiotic selection, a careful evaluation of the key determinants of a drug's tissue penetration like the molecular weight, lipophilicity, tissue to plasma penetration ratio, protein binding, and volume of distribution is recommended.<sup>35,51,52</sup>

## Older antibiotics

Vancomycin is effective against susceptible Gram-positive bacteria including MRSA,<sup>53</sup> and has shown comparable efficacy to newer agents (linezolid, daptomycin, tigecycline); however, poor tissue penetration (8%–10%) lowers its efficacy in severe cases of cSSTIs<sup>53</sup> (Table 4). The risk of nephrotoxicity and complications necessitates the need for dose titration in the special population with impaired renal function.<sup>54</sup> Clindamycin, active against MRSA, has

good tissue penetration (97%) and tolerability profile, and the ability to inhibit production of bacterial toxins common in CA-MRSA infection.<sup>27</sup> However, development of *Clostridium difficile*-associated colitis requires monitoring during therapy.<sup>55</sup> The use of penicillin derivatives and  $\beta$ -lactamase inhibitors (cloxacillin, amoxicillin/clavulanic acid) is discouraged in most cSSTIs cases due to lack of efficacy against MRSA infections. Also, fosfomycin and quinupristin/dalfopristin for cSSTIs use are challenged due to safety concerns of hepatic dysfunction, severe myalgia, and rapid emergence of resistance.<sup>53,56</sup> Inadequate evidence from controlled studies demonstrating efficacy and safety of older antibiotics for cSSTI also limit their clinical use.<sup>53</sup> With the advent of life-threatening MRSA and CA-cSSTIs, streamlining the use of available and effective antimicrobials becomes obligatory. Several national and international treatment guidelines have revisited the evidence to provide recommendations for antimicrobial therapy (Table 2).<sup>35</sup>

## Newer antibiotics

Newer antibiotics (refers to antibiotics which are approved by US FDA from 2000 onward) provide clinicians good opportunities to overcome current challenges in the management and treatment of MRSA infections (Table 4).

1. Linezolid, an oxazolidinone, is a newer alternative to glycopeptide antimicrobials, approved for use in serious cSSTIs caused by MRSA and VRE (US FDA approval: April 2000). It also inhibits bacterial exotoxins production that aggravates the severity of CA-MRSA infections.<sup>27</sup> Linezolid has demonstrated high clinical cure rates and non-inferiority to oxacillin/dicloxacillin in the treatment of cSSTIs, including cellulitis, skin abscesses, erysipelas, and surgical infections.<sup>57</sup> Linezolid also showed higher cure rates than vancomycin (67% vs 62%) against suspected MRSA-associated cSSTIs, and more recently, has demonstrated superior clinical and microbiological outcomes vs vancomycin.<sup>58–60</sup> In addition, equivalent oral bioavailability of linezolid offers a pragmatic advantage that facilitates shorter iv therapy and early hospital discharge.<sup>60</sup> Several studies have shown linezolid to be safe; however, in post-marketing studies, prolonged use of linezolid was associated with neuropathy (peripheral or optical), hematological abnormalities (particularly thrombocytopenia or anemia), and hyperlactatemia.<sup>61</sup>
2. Daptomycin, a cyclic lipopeptide approved for use in cSSTIs has shown adequate clinical activity against MRSA and VRE (US FDA approval: December 2003).

**Table 3** Minimum inhibitory concentration of antibiotics used for cSSTIs (European Committee on Antimicrobial Susceptibility Testing)

Drug	Pathogens	Minimum inhibitory concentrations ( $\mu\text{g/mL}$ )	
		Susceptible $\leq$	Resistant $>$
<b>Older Antibiotics</b>			
Vancomycin	<i>Staphylococcus aureus</i>	2	2
	Coagulase-negative staphylococci	4	4
	<i>Enterococcus</i> spp.	4	4
	Streptococcus groups A, B, C, and G	2	2
	<i>Streptococcus pneumoniae</i>	2	2
	Viridans group streptococci	2	2
	Gram-positive anaerobes except <i>Clostridium difficile</i>	2	2
	<i>C. difficile</i>	2	2
	<i>Corynebacterium</i> spp.	2	2
Amoxicillin/ clavulanic acid	<i>Aerococcus sanguinicola</i> and urinae	1	1
	<i>Enterococcus</i> spp.	4	8
	Viridans group streptococci	0.5	2
	<i>Haemophilus influenzae</i>	2	2
	<i>Neisseria meningitidis</i>	0.125	1
	Gram-positive anaerobes except <i>C. difficile</i>	4	8
	Gram-negative anaerobes	0.5	2
	<i>Helicobacter pylori</i>	0.125	0.125
	<i>Pasteurella multocida</i>	1	1
	<i>Kingella kingae</i>	0.125	0.125
	Enterobacteriaceae	8	8
<i>Enterococcus</i> spp.	4	8	
Clindamycin	<i>Staphylococcus</i> spp.	0.25	0.5
	Streptococcus groups A, B, C, and G	0.5	0.5
	<i>S. pneumoniae</i>	0.5	0.5
	Viridans group streptococci	0.5	0.5
	Gram-positive anaerobes except <i>C. difficile</i>	4	4
	Gram-negative anaerobes	4	4
	<i>Corynebacterium</i> spp.	0.5	0.5
Teicoplanin	<i>Enterococcus</i> spp.	2	2
	Streptococcus groups A, B, C, and G	2	2
	<i>S. pneumoniae</i>	2	2
	Viridans group streptococci	2	2
	<i>Staphylococcus</i> spp.	2	2
	Coagulase-negative staphylococci	4	4
<b>Newer antibiotics**</b>			
Linezolid	<i>Staphylococcus</i> spp.	4	4
	<i>Enterococcus</i> spp.	4	4
	Streptococcus groups A, B, C, and G	2	4
	<i>S. pneumoniae</i>	2	4
	<i>Corynebacterium</i> spp.	2	2
Daptomycin	Streptococcus groups A, B, C, and G	1	1
	<i>Staphylococcus</i> spp.	1	1
Tigecycline	Enterobacteriaceae	1	2
	<i>Staphylococcus</i> spp.	0.5	0.5
	<i>Enterococcus</i> spp.	0.25	0.5
	Streptococcus groups A, B, C, and G	0.25	0.5
Ceftaroline	<i>S. pneumoniae</i>	0.25	0.25
	<i>Haemophilus influenzae</i>	0.03	0.03
	Enterobacteriaceae	0.5	0.5
	<i>Staphylococcus</i> spp., <i>S. aureus</i>	1	1
Tedizolid	<i>Staphylococcus</i> spp.	0.5	0.5
	Streptococcus groups A, B, C, and G		
	Viridans group streptococci ( <i>S. anginosus</i> group)	0.25	0.25
Dalbavancin*	Viridans group streptococci ( <i>S. anginosus</i> group)	0.125	0.125
	<i>Staphylococcus</i> spp.	0.125	0.125
	Streptococcus groups A, B, C, and G	0.125	0.125
Oritavancin*	Viridans group streptococci ( <i>S. anginosus</i> group)	0.25	0.25
	<i>Staphylococcus</i> spp. ( <i>S. aureus</i> )	0.125	0.125
	Streptococcus groups A, B, C, and G	0.25	0.25

**Notes:** \*Dalbavancin and oritavancin are not approved in Singapore. \*\*"Newer antibiotics" refers to antibiotics which are approved by US FDA from 2000 onward. These data have been produced in part under ECDC service contracts and made available by EUCAST at no cost to the user and can be accessed on the EUCAST website [www.eucast.org](http://www.eucast.org). EUCAST recommendations are frequently updated and the latest versions are available at [www.eucast.org](http://www.eucast.org).

**Table 4** General features of older and newer antibiotics with activity against MRSA

Antibiotic	Dosage	Route of administration	Mode of action	Tissue penetration	Use in special population	Strengths	Limitations
<b>Older antibiotics</b>							
Vancomycin <sup>53</sup>	500 mg iv infusion for 60 minutes every 6 hours or 1 g iv infusion for 100 minutes every 12 hours	Intravenous	Bactericidal glycopeptide	8%–10%	Dose titration in patients with renal impairment	Gold standard for MRSA infections. Established efficacy and tolerability	Emerging resistance. Increasing MIC Poor tissue penetration
Clindamycin <sup>53</sup>	IV: 0.6–2.7 g infusion for 10–60 minute daily in 2–4 divided doses Oral: 150–300 mg every 6 hours, up to 450 mg in severe infections	Intravenous/oral	Bacteriostatic	95%	No dose adjustment in patients with renal impairment	Preferred agent for necrotizing fasciitis as it blocks bacterial toxin production	Emerging resistance <i>Clostridium difficile</i> -associated colitis
Cloxacillin <sup>122</sup>	Oral: 0.5 g every 6 hours IV: 1–2 g every 6 hours 2 g every 4 hours in case of severe infections	Oral/intravenous	Bactericidal	NA	No dose adjustment in patients with renal impairment	Main stream agent of treating methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	Lack of efficacy against MRSA infections
<b>Newer antibiotics</b>							
Linezolid <sup>123</sup>	600 mg IV or orally every 12 hours	Intravenous/oral	Bacteriostatic	105%	No dose adjustment in patients with renal impairment	Bioavailable as oral formulation Preferred agent for necrotizing fasciitis as it inhibits bacterial toxin production	Risk of toxicity with prolonged use Oral switch
Daptomycin <sup>124</sup>	4–6 mg/kg every 24 or 48 hours	Intravenous	Bactericidal	68%	No dose adjustment in patients with renal impairment	Once-daily iv regimen suitable for outpatient use	Emerging resistance
Tigecycline <sup>125</sup>	50 or 100 mg every 12 hours	Intravenous	Bacteriostatic	91%	No dose adjustment in patients with renal impairment	Broad spectrum activity against multidrug resistant Gram-positive and Gram-negative pathogens	Low serum levels
Ceftaroline <sup>126</sup>	600 mg iv infusion for 60 minutes every 12 hours	Intravenous	Bactericidal	NA	Dose titration in patients with renal impairment. No dose adjustments in obese patients	Good clinical efficacy and tolerability. Low propensity for <i>C. difficile</i> -related diarrhea	Low activity against Gram-negative pathogens. Bid or tid dosing
Tedizolid <sup>127</sup>	200 mg iv infusion for 60 minutes, once daily Oral: 200 mg once daily	Intravenous/ oral	Bacteriostatic	NA	No dose adjustment in patients with renal impairment	Bioavailable as oral formulation Preferred agents for necrotizing fasciitis as it inhibits bacterial toxin production	Lower risk of myelotoxicity and drug–drug interactions. Oral switch
Dalbavancin <sup>68*</sup>	1,000 mg iv infusion for 30 minutes	Intravenous	Bactericidal	NA	Dose titration in patients with renal impairment	Long half-life allowing once-daily iv administration suitable for outpatient use	Low activity against Gram-negative pathogens. Cannot be cleared by hemodialysis in case of toxicity
Oritavancin <sup>68*</sup>	1,200 mg single dose iv infusion for over 3 hours	Intravenous	Bactericidal	NA	Dose titration in patients with renal impairment	Long half-life allowing once-daily iv administration	Early discharge Low activity against Gram-negative pathogens

**Notes:** Dosage approved in Singapore mentioned in the table, except for dalbavancin and oritavancin. <sup>68</sup>Dalbavancin and oritavancin are not approved in Singapore.

**Abbreviations:** MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available.



Real-world data collected across wide geographical regions (US, Europe, Latin America, and Asia) demonstrated high clinical success rates (81%) with daptomycin for cSSTIs.<sup>62</sup> Daptomycin showed non-inferiority to vancomycin and semi-synthetic penicillins in the treatment of cSSTIs.<sup>63</sup> In an open-label study, 77% of 53 cSSTIs patients treated with daptomycin achieved complete resolution of infection (vs 42% of 221 patients on vancomycin) with rapid symptom resolution in a shorter inpatient treatment course.<sup>64</sup> The overall efficacy and safety, with the practical advantage of a once-daily intravenous (iv) regimen, supports the use of daptomycin in cSSTIs.<sup>65,66</sup> Overall, daptomycin has a good safety profile; however, clinical studies have reported elevations in creatine phosphokinase and associated muscle toxicity. Therefore, monitoring of laboratory abnormalities is recommended during treatment.<sup>67</sup>

3. Tigecycline, a tetracycline-related antimicrobial, is an advantageous empiric treatment option for cSSTIs (US FDA approval: June 2005). In 2013, the US FDA issued a black box warning of increased risk of mortality of tigecycline vs comparator drugs. However, tigecycline may likely be considered instead of combination therapy, where this is deemed necessary, due to its broad-spectrum activity (Table 4).<sup>68</sup>
4. Ceftaroline, a new generation cephalosporin with clinically meaningful activity against MRSA, is approved for the treatment of cSSTIs and community-acquired pneumonia (US FDA approval: October 2010). Over 90% of MRSA isolates were found to be susceptible to ceftaroline in US, Europe, Middle East, and Africa with MICs ranging from 0.25 to 4 mg/L. Ceftaroline has also shown potent antimicrobial activity against a large number of SSTI-associated bacterial isolates including MRSA (80.6% susceptibility) from South Africa and Asia-Pacific region.<sup>69</sup> The pharmacodynamic profile of ceftaroline 600 mg every 8 hours (q8h) and every 12 hours (q12h) infusion was generally comparable and is adequate for the effective eradication of MRSA. The q8h infusion treatment had a higher probability of attaining MIC of 4 mg/L; however, this treatment approach has limited evidence from clinical studies and is yet to receive approval in this region. The safety profile of ceftaroline was consistent with cephalosporin class. The most common adverse events observed were diarrhea, nausea, and rash.<sup>70</sup> Administration of ceftaroline demonstrated no significant effect on the intestinal flora in healthy participants, and thus, risk of *C. difficile*-related diarrhea is low.<sup>71</sup> Ceftaroline (q12 dosing schedule) is a viable option in the armamentarium of antibiotics for treating cSSTIs due to Gram-negative and Gram-positive (with MRSA) infections or following failure of vancomycin therapy (Table 4).<sup>72</sup> Studies with a q8h dosing of ceftaroline are ongoing; if the findings are conducive, this dosing may become a better alternative than the standard dose, especially in areas of high MRSA endemicity.
5. Tedizolid, another novel oxazolidinone is approved for use in ABSSSI due to MRSA (US FDA approval: June 2014).<sup>73</sup> In two Phase III studies of ABSSSI, a 6-day course with tedizolid was significantly non-inferior to a 10-day linezolid course for an early clinical response (48–72 hour after treatment initiation).<sup>74</sup> A better tolerability profile (few gastrointestinal adverse events, lower myelotoxicity risk) and an option of iv-to-oral switch make tedizolid a valuable treatment choice for management of cSSTIs.<sup>74</sup> The oxazolidinones are particularly helpful for the treatment of necrotizing fasciitis since they inhibit the production of bacterial pyrogenic endotoxins.<sup>75</sup>
6. Oritavancin and dalbavancin are lipoglycopeptides (approved by US FDA in 2014) with the pharmacokinetic advantage of extended plasma half-life, enabling single-dose regimens.<sup>68</sup> These antibiotics are yet to receive approval in Singapore. Oritavancin, a derivative of vancomycin, has extended bactericidal activity against MRSA and daptomycin non-susceptible VRE. Single iv dose, oritavancin, was non-inferior to twice-daily vancomycin (7-to-10 day course) in two Phase III studies of ABSSSI caused by Gram-positive pathogens.<sup>76,77</sup> Dalbavancin, a derivative of a teicoplanin-like natural antibiotic has antimicrobial activity against almost all clinical MRSA isolates. Once-weekly iv dalbavancin was non-inferior to twice-daily vancomycin followed by oral linezolid with comparable success rates in ABSSSI as demonstrated in a pooled analysis.<sup>78</sup> Dalbavancin and oritavancin has a similar safety profile as vancomycin. In clinical studies, the most commonly reported adverse events were headache, nausea, diarrhea, and vomiting.<sup>79</sup> The elimination of multidose and multiday regimen and lower propensity for resistance development are potential benefits of dalbavancin and oritavancin treatments. However, the absence of de-escalation, high-cost acquisition, and limited clinical evidence for these agents is noteworthy.<sup>68</sup>

## Intravenous-to-oral switch

For the rapid attainment of desired serum therapeutic levels, parenteral antibacterial therapy is recommended for cSSTIs

in hospitalized or ambulatory care settings.<sup>34</sup> Oral formulations with convenient dosing and administration at home offer effective outpatient management, allow a seamless transition of continued care, and recovery. Potent antibiotics with high oral bioavailability offer an additional advantage without compromising clinical efficacy (eg, linezolid, tedizolid). The key advantage of iv-to-oral switch is early hospital discharge, which from a physician's perspective lowers risks of HA complications and infections.<sup>35,80</sup> From a patient's perspective it results in reduced isolation, early recovery, and improved quality-of-life.<sup>35,81</sup> The critical decision of switching a patient from iv-to-oral therapy depends on the patient's ability to tolerate the switch and on the microbiological etiology.<sup>82</sup> Afebrile (>24 hours) patients with clinically stable infection, normalized WBC count (<4×10<sup>9</sup>/L or >12×10<sup>9</sup>/L), no cardiovascular abnormality (no tachycardia and systolic blood pressure ≥100 mgHg) and who have received iv antibiotic therapy for >24 hours can be switched to oral therapy. Patients should be able to tolerate oral fluids or diet to allow administration of oral medications with no gastrointestinal complications.<sup>35,83</sup> The switch to oral therapy is contraindicated in patients with severe vomiting and diarrhea, hematological malignancies or neutropenia, impaired gastrointestinal absorption, dementia, and severe infections of the musculoskeletal, central nervous system, or vascular systems.<sup>35,83</sup> Presence of comorbidities, unavailability of caregiver, and an advancing age may commonly delay oral switch and hospital discharge.<sup>35</sup>

## De-escalation strategy

Antibiotic de-escalation is a scheme of utilizing a discreet antibiotic regimen to avoid indiscriminate antibiotic use that increases the risk of resistance.<sup>84</sup> The de-escalation strategy can be implemented by switching from empirical broad-spectrum antimicrobials to a narrower-spectrum or targeted treatment after a systematic reassessment.<sup>85</sup> Currently, the acceptable approach is the timely initiation of antibiotic therapy that provides appropriate coverage for key pathogens including resistant strains, followed by a de-escalation approach on the availability of susceptibility results to avoid prolonged exposure to a broader-spectrum antibiotic therapy.<sup>84</sup> Available evidence indicates that antibiotic de-escalation has no safety concerns, showed improved clinical outcomes (based on microbiological data, novel inflammatory markers), lesser antibiotic resistance profiles, and lowered chances of recurrent infections along with substantial reductions in adverse effects of non-judicious use of antibiotics.<sup>86,87</sup>

The de-escalation strategy aims to reduce costs and duration of hospitalization by switching from empiric antibiotics to definitive culture-directed agents, curbing unnecessary or

redundant treatment, and switching from iv to oral therapy. This switch to oral therapy also results in direct cost savings (supplies, nursing time, cost-effective drug), lowers risk of line infections (via the catheters), and increases the patient's mobility, thereby reducing the duration of hospital stay.<sup>88</sup> Protocols that guide transitioning to more effective antimicrobials with reduced toxicity (eg, β-lactams instead of vancomycin for confirmed MSSA) may ease selection pressures and help achieve appropriate and safe de-escalations for critical infections.<sup>89</sup> The duration of antibiotic use (less by 2 days) and the length of stay were significantly reduced in patients with ABSSSIs subjected to Antimicrobial Stewardship Program (ASP)-based intervention. The reduction in length of hospital stay culminated into a substantial cost reduction.<sup>90</sup>

Development of *C. difficile*-associated diarrhea following exposure to most antibiotics is a more predominant public health problem as compared with antimicrobial resistance.<sup>91</sup> Therefore, another critical target for ASP should be preventing infection or restricting nosocomial infections with *C. difficile* in susceptible individuals. The incidence of *C. difficile* infections can be considerably lowered by optimizing the selection of antibiotics (eg, possibly substitution with newer cephalosporins like ceftaroline), dosing, de-escalation, and duration of therapy.<sup>88,91</sup>

## Antimicrobial stewardship program

ASP is a strategy to improve the current antibiotic prescription practice through education of prescribers, development of antimicrobial formulary, and review-feedback process of the prescription pattern for prescribers.<sup>92,93</sup> Excessive or indiscriminate use of antibiotics, particularly the broad-spectrum antibiotics, is associated with the emergence of antibiotic-resistant bacteria such as ESBL-producing Gram-negative bacteria, MRSA, and development of *C. difficile* infections. A multifaceted strategy is required to combat the antimicrobial resistance. ASP, a multidisciplinary approach, encourages various measures, including optimization of prescribing practice. It mainly aims to improve the clinical outcomes of antibiotic use, minimize the adverse effects, and impede the development of antimicrobial resistance and *C. difficile* infections.<sup>94</sup> Several countries have successfully adopted ASP in hospital settings based on the WHO Global Action Plan (mandated in May 2015) to tackle antimicrobial resistance.<sup>95</sup> ASPs implemented by the National Health Service (NHS) across the UK utilizes "Start Smart-Then Focus" approach to improve prudent use of antibiotics.<sup>94,96</sup> It comprises several strategies, including implementation of evidence-based local prescribing guidelines relevant to local health care setting and

antibiotic resistance pattern, iv-to-oral switch, de-escalation, dose optimization, quality assurance audits, education, and training.<sup>96</sup> These strategies have substantially supported the improvement in discreet antibiotic usage, reduced length of hospital stay, and improved clinical outcomes, such as reductions in *C. difficile* infections.<sup>97,98</sup> Hospital settings in Singapore employ a similar ASP model of iv-to-oral switch and de-escalation. A 3-year retrospective review from Singapore General Hospital revealed that patients with ABSSSI had an acceptance rate of 66% for the interventions recommended by the ASP and these interventions caused no safety concerns.<sup>99</sup> Nevertheless, to improve the overall success in hospital stays and for patient safety, regular review and upgrading of ASPs with a holistic health care approach is advisable.

## Nursing and postoperative wound management

Optimal management of wounds is critical to prevent potential complications in postoperative surgical sites or dehiscence of the surgical wounds and improve recovery with appropriate functional and esthetic results in patients with cSSTIs.<sup>100</sup> Wound dressings aid wound healing by maintaining a moist environment (accentuates wound re-epithelization and healing), provide a barrier against bacterial or fluid contamination, and help in the removal of excessive exudate (by absorbing, gelling, and transfer of

fluid away from the wound bed), preventing likely wound maceration (Figure 2).<sup>100,101</sup>

Advanced therapies in the wound management such as silver compound dressing and negative wound pressure treatment may improve the wound care by decreasing the chances of reinfection and help in the removal of exudate, reduction of lateral incision tension, and reduction of hematoma or seroma formation.<sup>43,102–104</sup> Silver and silver compounds have broad-spectrum bactericidal properties and have been used effectively as wound dressings.<sup>105</sup> Sustained-release silver dressings, silver-donating nanocrystalline dressings, and antimicrobial negative-pressure dressing (NPD) with silver have proven to be effective in promoting wound healings.<sup>106–108</sup> Use of silver-based dressing in packing abscess cavities after incision and drainage treatment may cause faster healing along with improvements in pain intensity.<sup>109</sup> Silver dressings have proven to be safe and effective as compared to normal gauze dressings in preventing postoperative surgical site infections.<sup>106,110</sup>

Physical methods of exudate control in infected post-surgical wounds such as negative wound pressure therapy or a combination of a silver antimicrobial NPD have demonstrated to improve healing outcomes along with decreased nursing time and reduced cost.<sup>41,111,112</sup> In cases of minor dehiscence, secondary closure of wounds following removal of necrotic tissue must be opted. For severe dehiscence, TNP therapy following local debridement is recommended.<sup>100</sup> Selection

### Wound dressing

- Provides moist environment for wound healing
- Barrier against bacterial contamination
- Removal of exudates
- Antimicrobial dressings: preferred in excess exudate with bacterial infection

### Silver/silver compound dressing

- Bactericidal agents
- Broad-spectrum
- Sustained-release dressing
- Nanocrystalline silver dressing: reduces inflammation by lowering levels of proteolytic enzymes that delay wound healing
- Silver antimicrobial + negative pressure dressing: management of superficial to partial-thickness burns, wounds, abrasions, traumatic wounds, surgical wounds, dehisced wounds, diabetic ulcers, and venous ulcers

### Physical methods

- Negative pressure wound therapy (for heavily exudating wounds): reduces edema, improves tissue perfusion by reducing size and complexity of wound
  - Silver antimicrobial negative pressure dressing + negative pressure wound therapy: improved healing
- Secondary wound closure: minor dehiscence of surgical wounds
- Topical negative pressure: severe dehiscence of surgical wounds

**Figure 2** Nursing and postoperative care in complicated skin and soft tissue infections.

of appropriate methods of cleansing and dressing along with prompt intervention of wound complications holds the key to effective wound management.

## Future directions

A myriad of antibiotics is already available and a number of novel ones have been or are being developed for the management of cSSTIs. Clear differentiation, in terms of therapy outcomes, among these newer agents is hampered by the lack of robust clinical data on head-to-head comparison between these antibiotics. Although newer antibiotics may confer several advantages over older agents, they are in general expensive and less accessible. Furthermore, data regarding their usage in special populations, eg, diabetic foot infections, peripheral vascular disease, etc, is inadequate.<sup>113</sup> Special indications for these newer agents such as oxazolidinones can be regarded as preferred agents for necrotizing fasciitis because they inhibit bacterial toxin production.<sup>75</sup> Ceftaroline offers additional advantages with possible lower risk for *C. difficile* infection. Additionally, there are emerging data on combination with older antibiotics to achieve synergistic efficacy and cost-effectiveness in therapy. Studies exploring vancomycin and beta-lactam combinations for MRSA have demonstrated shortening of the duration of MRSA bacteremia.<sup>114,115</sup> Nonetheless, larger sample size, double-blind, adequately powered future trials with clinically relevant end points for newer antibiotics and newer combinations of antibiotics for cSSTIs are required to fill the information gaps for clinicians to augment decision making.<sup>116</sup> Real-world evidence would further add to the information on safety, efficacy, and cost-effectiveness of these therapies for cSSTI management.<sup>117</sup> In short, a prudent clinical decision on the selection of the most appropriate pharmacological agent or agents would be based on their efficacy, safety profile, tolerability, cost-effectiveness, accessibility, and practicability.

## Conclusion

In the light of epidemiological shift in global prevalence of MRSA and associated cSSTIs, clinicians need to constantly challenge and review the existing clinical guidelines and practices. With the emergence of newer antibiotics and current medical evidence in clinical practice, optimal clinical usage needs to be determined. Decision on the choice of antimicrobial therapy for cSSTI is guided by both scientific data and clinical experience. Multiple factors, including host factors, local multidrug resistance data, cost consideration, and drug characteristics, have to be considered holistically

in the management of cSSTIs. Often, the outcomes, despite prudent clinical judgment, remain unpredictable. Simply, other factors at play that may not be within the clinician's scope of knowledge could also impact treatment outcomes. Local ASP strategies in health care institutions would guide clinicians in early initiation of specific treatments to combat region-specific CA-MRSA infections. Hence, adopting well-tested approaches such as iv-to-oral switch, regular review of clinical response, de-escalation to narrow-spectrum antibiotics to reduce the length of hospital stay, hospital-related complications, and overall treatment expenses can modify the paradigm and the clinical outcomes for management of cSSTIs in countries like Singapore.

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